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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/702,459	11/07/2003	Mitsuhiro Okuda	61352-058	9724

7590 03/29/2006

Michael E. Fogarty
McDERMOTT, WILL & EMERY
600 13th Street, N.W.
Washington, DC 20005-3096

EXAMINER	
VANIK, DAVID L	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,459	OKUDA ET AL.	
	Examiner	Art Unit	
	David L. Vanik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11,13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11,13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Applicant's Request for Continued Examination filed on 12/21/2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-11, 13, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin, does not reasonably provide enablement for the formation of a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of any protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims; nature of the invention; state of the prior art; amount of direction provided by the inventor; the level of predictability in the art; the existence of working examples; quantity of experimentation needed to make or use the

invention based on the content of the disclosure; and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: Claims 1, 4-11, 13, and 16 are drawn to a method of forming a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of any protein. Considering the vast number of possible proteins with a "cavity," this is a very broad claim, one that is not supported by the instant specification.

The nature of the invention: In contrast to what is claimed, the invention is drawn to a method of producing a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin. The use of only apoferritin as the nanoparticle/protein is consistent with the disclosure of the instant specification (see pages 23-54). The rejected claims 1, 4-11, 13, and 16, however, are drawn to a much broader invention, a method of forming a nanoparticle by using any protein with a cavity.

The amount of direction provided by the inventor: There is nothing in the specification that would indicate that the current method would work with any protein with a cavity. Proteins with a "cavity" comprise a very broad class of species. Along these lines, guidance for preparing a nanoparticle composition by utilizing the cavity of any protein is not provided in the instant specification. With respect to the instant method, there is a substantial gap between a method of producing a nanoparticle using

apoferritin and a method of producing a nanoparticle using any protein with a cavity. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

State of the prior art: As confirmed by US 5,304,382 ('382), metal ions such as copper, chromium, and nickel are capable of being incorporated into an apoferratin protein shell (abstract and column 4, lines 52-68). '382 does not, however, disclose the effectiveness of incorporating metal ions, such as copper, nickel, and chromium, into proteins with other such cavities. Given this, one of ordinary skill in the art would be forced to experimentally discover which particular protein with a cavity could be used to incorporate either nickel, chromium, or copper without guidance from the instant disclosure or the prior art.

The presence or absence of working examples: Twenty-five examples are included in the instant specification, all of which disclose methods of forming nanoparticles by utilizing the cavity of apoferritin. Applicant fails to provide examples of methods of forming nanoparticles by utilizing the cavity of any other protein. As such, the practitioner would turn to trial and error experimentation in order to form a nanoparticle by utilizing the cavity of a protein other than apoferritin, without guidance from the specification or the prior art. This is heightened by the fact that metal ions, such as copper, have the ability to coordinate and bind with a variety of protein sites (See Thomas Creighton, "Proteins", page 362). Given this, one of skill in the art would be faced with a burdensome amount of research in order to practice the instant method with a protein with a cavity other than apoferritin.

The quantity of experimentation: In the instant case, there is a substantial gap between a method of producing a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin and a method of forming a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of any protein. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-11, 13, and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin at a very specific pH range and buffer concentration, does not reasonably provide enablement for the formation of a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin at any alkaline pH range. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims; nature of the invention; state of the prior art; amount of direction provided by the inventor; the level of predictability in the art; the existence of working examples; quantity of experimentation needed to make or use the invention based on the content of the disclosure; and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: Claims 1, 4-11, 13, and 16 are drawn to a method of forming a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of any protein by mixing a first and second solution, wherein said first solution contains a protein with a cavity part, **an alkaline buffer solution**, and a metal ion selected from nickel, chromium, or copper, and said second solution contains a carbonate or hydrogen carbonate ion. Considering the teachings of the instant disclosure, this is a very broad claim, one that is not supported by the instant specification.

The nature of the invention: In contrast to what is claimed, the invention is drawn to a method of forming a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin by mixing a first and second solution, wherein said first solution contains a protein with a cavity part, **a buffer with a very specific pH**, and a metal ion selected from nickel, chromium, or copper, and said second solution contains a carbonate or hydrogen carbonate ion. (see pages

23-54). The rejected claims 1, 4-11, 13, and 16, however, are drawn to a much broader invention, a method of forming a nanoparticle by using any protein with a cavity **at any alkaline pH**.

The amount of direction provided by the inventor: There is nothing in the specification that would indicate that the current method would work with any protein with a cavity at any alkaline pH. As a general matter, the solubility of proteins is very complicated, and is determined by a variety of factors such as the pH of the solution, the isoelectric point of the protein, ionic strength of the solution, and the solvent (See Thomas Creighton, "Proteins", pages 262-264). This is further confirmed by examining the instant disclosure (see pages 23-54). For example, when nickel is used as the metal ion, the pH of the solution is between 8 and 9 and preferably between 8.3 and 8.65 (see page 8, lines 4-11). Further complicating the issue is the fact that the precipitation points of nickel sulfate, for example, tend to vary as a function of concentration (page 37, 25-29). According to the instant specification (page 42, line 21 – page 43, line 1), apoferritin tends to aggregate when the pH of the solution rises to a level above 8.65. Thus, it appears that the instant method of forming a nanoparticle by incorporating nickel into an apoferritin cavity only works under a very defined set of conditions. In terms of producing a chromium compound-apoferritin complex, having a HEPES buffer at a pH of 7.5 (500mM) in combination with a MES buffer at pH 5.5 (500mM) appears to be suitable (page 49). No other conditions are specified within the instant specification. With respect to incorporating copper into apoferritin, a MES buffer at pH 6.0 (500mM) appears to be suitable.

Given the instant disclosure, guidance for preparing a nanoparticle composition by utilizing the cavity of any protein at any alkaline pH is not provided in the instant specification. With respect to the instant method, there is a substantial gap between a method of producing a nanoparticle using apoferritin and a metal ion at a very specific pH range and buffer concentration and a method of producing a nanoparticle using any protein with a cavity at any alkaline pH. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

State of the prior art: As stated above, as a general matter, the solubility of proteins is very complicated, and is determined by a variety of factors such as the pH of the solution, the isoelectric point of the protein, ionic strength of the solution, and the solvent (See Thomas Creighton, "Proteins", pages 262-264). Given this, one of ordinary skill in the art would be forced to experimentally discover which protein with a cavity could be used to incorporate either nickel, chromium, or copper at an unspecified pH and buffer concentration range without guidance from the instant disclosure or the prior art. This would place an undue burden on one of skill in the at to practice the invention commensurate in scope with the claims.

The presence or absence of working examples: Twenty-five examples are included in the instant specification, all of which disclose methods of forming nanoparticles by utilizing the cavity of apoferritin. For the incorporation of nickel ions into apoferritin, a pH between 8 and 9 appears to be essential. The conditions for inculpating either chromium or copper ions into apoferritin are further specified on pages 47-54. Applicant fails to provide examples of methods of incorporating nickel,

chromium, or copper into apoferritin over a broad range of "alkaline buffer solution" conditions. As such, the practitioner would turn to trial and error experimentation in order to form a nanoparticle by utilizing the cavity of a apoferritin at any alkaline pH, without guidance from the specification or the prior art. Given this, one of skill in the art would be faced with a burdensome amount of research in order to practice the instant method as claimed without guidance from the instant specification.

The quantity of experimentation: In the instant case, there is a substantial gap between a method of producing a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin in an alkaline buffer and a method of forming a nanoparticle in which a metal ion chosen from nickel, chromium, or copper is incorporated into the cavity of apoferritin in a buffer of a well-defined pH and concentration. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Response to Arguments

Applicant's arguments with respect to claims 1, 4-11, 13, and 16 have been considered but are moot in view of the new ground(s) of rejection.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David L. Vanik whose telephone number is (571) 272-3104. The examiner can normally be reached on Monday-Friday 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Vanik, Ph.D.
Art Unit 1615

3/17/06

CARLOS A. AZPURU
PRIMARY EXAMINER
GROUP 1500